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Diagnostic Ultrasound

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CHAPTER 3

Contrast Agents in Diagnostic Ultrasound

• Pamela L. Hilpert, M.D., Ph.D.

FREE GAS BUBBLES
ENCAPSULATED GAS BUBBLES
COLLOIDAL SUSPENSIONS
Collagen or Gelatin Spheres
IDE Particles
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LIPID EMULSIONS
AQUEOUS SOLUTIONS
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Great strides have been made both in the development and in the method of administration of contrast agents to opacify the lumen of bowel, veins, arteries, bile ducts, and ureters. Contrast agents are routinely administered orally and intravenously to enhance the small differences in roentgenographic attenuation between normal and abnormal tissues, and to assess organ function for intravenous urography, computed tomography, nuclear medicine and magnetic resonance imaging.

Administered contrast is not new to the field of ultrasound. Nonvascular applications are common in day to day practice. Water can be introduced into the bowel lumen orally to distinguish a fluid-filled stomach from a left upper quadrant collection[1] and rectally to distinguish a large-bowel collection from a pelvic collection.[2] Microbubbles produced by the injection of small quantities of agitated saline can be used to confirm the location of biopsy needles and catheters during interventional procedures.[3,4] Intravenous contrast agents were first introduced to ultrasound more than two decades ago,[5,6] but progress has been slow and sporadic, limited to right-sided cardiovascular imaging by the lack of a clinically suitable agent for other vascular or abdominal uses.

Intravenous ultrasound contrast agents are substances introduced into the vascular system to enhance contrast differences between normal and abnormal tissue or to enhance arterial or venous Doppler signal. Contrast agents may be specifically devised to best address certain clinical situations. For imaging of the liver and spleen, preferential biodistribution or tissue uptake by the reticuloendothelial system or by hepatocytes is advantageous. Contrast agents may aid in tissue characterization with the development of tissue-specific or tumor-specific agents. An agent may also be designed for use in a functional study to measure uptake and clearance of the organ-specific agent. For Doppler interrogation, identification of tumor vasculature may be an arduous task and a long-lived agent that is capable of recirculating in the bloodstream is required. For determinati n f vascular patency or for venous imaging, an agent with a relatively short half-life can be used. Contrast agents may also be introduced into the lumen of an rgan (e.g., uterus and fallopian tubes) to outline a cavity, determine patency, or identify a fistula.

To be effective, the contrast agent must be stable for a sufficient period to be imaged. The substance must be metabolized or removed from the circulation in a prompt fashion. It must have low toxicity, so that a quantity sufficient to produce the desired effect can be administered. Finally, the physical properties of the contrast agent must produce an identifiable alteration in acoustic parameters of the tissue under examination.

Contrast agents can be classified into several groups, including free gas bubbles, encapsulated gas bubbles, colloidal suspensions, lipid emulsions, and aqueous solutions.[7,8] These agents may improve contrast resolution among various tissues by alteration of one or m re of the acoustic parameters of tissue:

- the backscatter or echogenicity
- the attenuation or degree of beam penetration
- the speed of sound propagation through tissue

FREE GAS BUBBLES

Free gas bubbles are excellent scatterers of the ultrasound beam because of the large impedance mismatch between gas and surrounding body tissues. Gas bubbles may pre-exist in solutions,[9,10] result from vigorous shaking during preparation,[10] or occur with a change in temperature of the solution (e.g., the vaporization of ether at body temperature),[11] through cavitation at the catheter tip following a rapid, high-volume injecti n,[9] or through ultrasonic microcavitation.[12-14] The uses f

free gas bubbles are limited because free bubbles are relatively large (10 to 100 μm), short-lived, and effectively removed by the pulmonary capillary circulation.[15,16] Smaller bubbles, capable f traversing the pulmonary bed (<8 μm), have high surface tension and high internal pressures, leading t dissolution before the pulmonary bed is reached.[17] For these reasons, free gas bubbles are only suitable for the delineation of right sided cardiac structures and intracardiac shunts.

Gramiak et al[5,6] first described the use of solutions containing free gas bubbles as ultrasound contrast agents. Rapid injections directly into the aortic root or cardiac chambers allowed specific anatomic validation of the origin of M-mode ultrasound images by the production of an intense cloud of echoes at the site of injection. These microbubbles were produced in various solutions (indocyanine green, 5% dextrose, saline or autologous blood), probably during the injection phase as a result of cavitation occurring at the catheter tip. Cavitation bubbles refer to solubilized gases that transiently come out of solution because of the large pressure changes produced during rapid high-volume injections.[9] Meltzer et al[10] later found that with clinically used catheter sizes (19- to 23-gauge) and forceful hand injections, cavitation bubbles played no significant role in echo enhancement. The amount of microbubbles contained in the solution before injection was responsible for the ultrasound contrast effect. Later studies supported this notion in that hand agitation of solutions before injection produced a more striking contrast effect, probably because of the larger number of microbubbles in the fluid.[13,14,16,18]

Ziskin et al[11] demonstrated enhanced Doppler signal from arteries following intra-arterial injections of a variety of substances, including Renografin, carbonated water, and ether. Ether, which boils at body temperature, releasing gas bubbles, produced the most intense Doppler enhancement.

Since that time, sonication of solutions has been used to produce smaller, more uniform microbubbles.[12-14,18] Sonication, or the deposition of ultrasound energy to produce transient cavitation bubbles in solutions, is able to produce microbubbles of less than 10 μm in high-osmolarity, high-viscosity solutions such as 70% sorbitol or dextrose. More dilute, less viscous solutions produce larger microbubbles, ranging in size from 10 to 23 μm. The high surface tension of these small microbubbles can be reduced through the use of surfactants or other stabilizers. These microbubbles are more resistant to intravascular collapse[12,19] and have less tendency to coalesce.[10,20]

Opacification of the left atrium and left ventricle has been reported following injection of sonicated Ren grafin r sorbitol from the pulmonary capillary wedge position, probably resulting from transit time being short enough for the microbubbles to survive.[21,22] Otherwise, free gas bubbles produced by hand agitation or sonication play little role in left-sided cardiac imaging or pacification of the systemic arterial tree because of the short life span and instability f smaller bubbles. Intra-arterial injecti ns are possible, but may cause the embolization of larger particles and are contrary to the noninvasive nature of the abdominal ultrasound examination.

SH U 454* is a gas-containing contrast agent that shows great promise for both intravenous and intracavitary uses. This agent is a powdered polysaccharide that, when mixed with a diluent, forms a crystalloid-microbubble suspension.[23-25] The crystals have varied shapes and range in size from 1 to 10 μm (medium 3.5 μm).

The mechanism of increased echogenicity is currently unknown, but trapping of gas bubbles between crystals, vaporization of water as the materials diss lve in the blood, and enhanced reflectance of the crystals have been postulated. The carrier substance, galactose, which is quickly metabolized by the liver, is tolerated well without severe side effects or toxicity. Initial work with SH U 454 has been limited to the imaging of right heart structures[23-25] and intracavitary injections[25-30] because of particle instability. Following injection, the particles dissolve within several seconds because of the concentration and temperature gradient within the bloodstream. A more stable agent, SH U 508, is currently under investigation and shows great promise for left-sided cardiovascular imaging[31,32] and systemic arterial Doppler after intravenous injection.[33]

SH U 454[34] has shown improved detection of liver tumors in rats following hepatic arterial or portal venous injections. Only 21% of induced hepatomas were visible on noncontrast sonography while 71% were detected as a hypoechoic mass with contrast administration. Contrast-enhanced sonography may improve hepatic tumor detection during intraoperative procedures.

Intracavitary uses of SH U 454 have also been described. Fallopian tube patency could be well assessed by contrast-enhanced transvaginal ultrasound-guided hysterosalpingography.[26-30] In human trials, a hysterosalpingogram was performed with SH U 454 as the agent and vaginal sonography for imaging. Fallopian tube patency was accurately determined following transcervical instillation of SH U 454 by visualizing the echogenic material fill the uterine cavity and flow through the tubes[8] (Fig. 3-1). Color or duplex Doppler ultrasound allowed direct assessment of flow of the contrast agent within the uterine cavity and tubes with improved accuracy over traditional radiographic hysterosalpingography imaging alone[27,30] (Fig. 3-2). Results

*Echovist, Schering AG, Berlin, Federal Republic of Germany

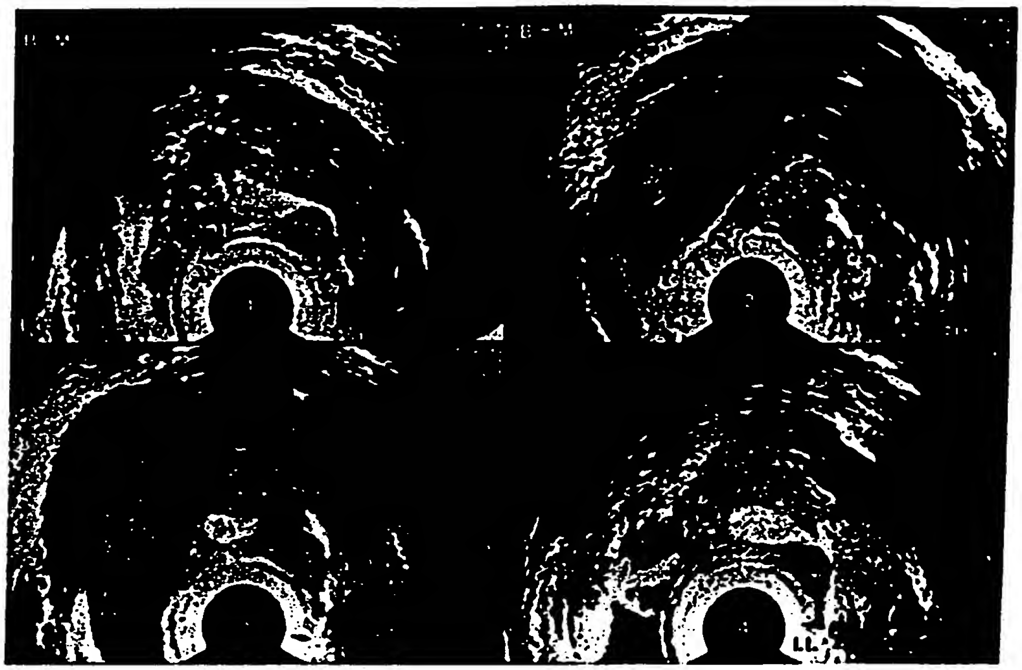


FIG 3-1. Transvaginal hysterosalpingo-contrast-sonography using SH U 454 through the cervical canal. *(1)* Longitudinal section of the uterus *(U)* filled with SH U 454; *(2)* Lumen of right tube *(RT)* perfused *(arrow)*, cross-section of fundus uteri *(arrowhead)*; *(3)* Lumen of left tube perfused *(arrows)*, cross section of fundus uteri; *(4)* Transfer of contrast medium from cavum uteri (cross-section) to the pars intramularis of left tube *(LT)*.
(From Deichert U, Schlief R, van de Sandt M, et al, with permission.)

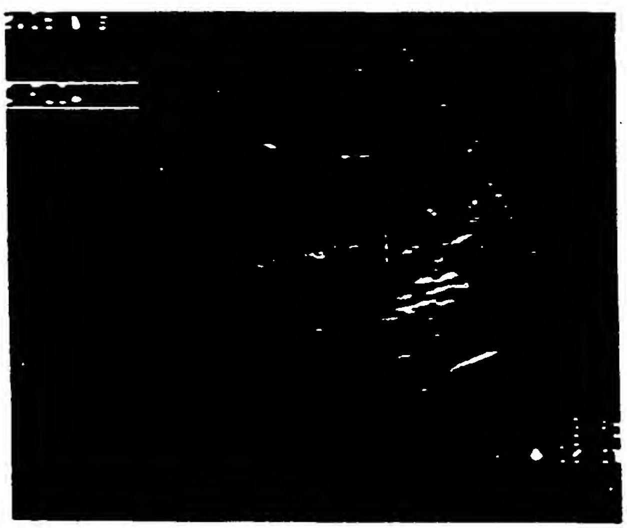


FIG 3-2. Color Doppler-assisted transvaginal-hysterosalpingo-contrast-sonography using SH U 454. Transverse image of the uterus shows enhanced color Doppler signal in the area of both tubes.
(Courtesy of Reinhard Schlief, Berlin, Federal Republic of Germany.)

were highly correlated with conventional radiographic hysterosalpingography and laparoscopy, without the risks of radiation exposure, anesthesia or a laparoscopy. Transvaginal ultrasound-guided hysterosalpingography may be a simple method of screening for tubal patency.

Real-time ultrasound and Doppler have revolutionized the diagnosis of peripheral venous disease. However, the varied appearance of venous thrombosis poses difficulty in the identification of intraluminal filling defects. Slow flow, low signal-to-noise ratios, and inability to compress central veins such as the inferior and superior vena cava, limit the evaluation of venous hemodynamics. SH U 454 has been used to increase the echogenicity of blood, producing improved diagnosis of venous thrombosis (residual lumen, recanalization), venous valvular insufficiency, and varicosities[35] (Fig. 3-3).

ENCAPSULATED GAS BUBBLES

To overcome the size and stability limitations of free gas bubbles, encapsulation of bubbles was proposed. Although initial attempts at encapsulation produced large bubbles that cl gged the capillary tree, the utility f this notion was clearly dem nstrated. Carroll et al[36,37] produced nitrogen microbubbles encapsulated within a thin gelatin coating (gelatin encapsulated nitr gen

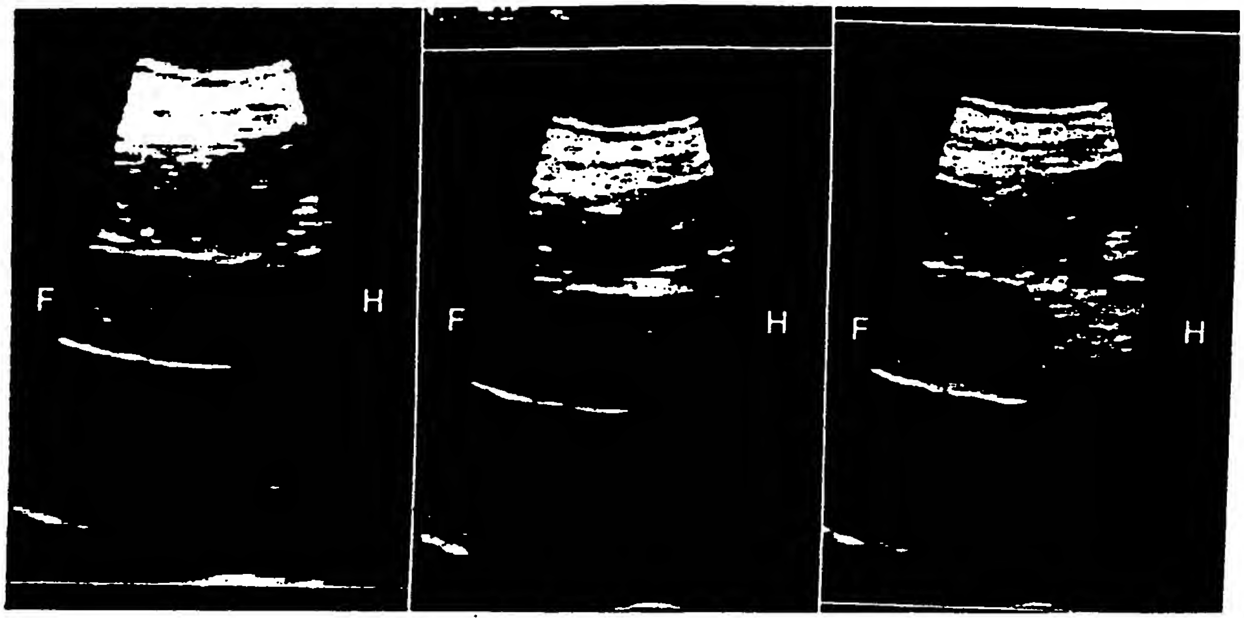


FIG 3-3. SH U 454 outlining the caudal vena cava. A, Following a femoral venous injection of SH U 454, the bolus of echogenic contrast agent is noted to arrive in the caudal vena cava of a dog. B, Several seconds later, the echogenic contrast agent fills entirely the lumen of the vena cava. C, Still later, nonopacified blood enters the caudal vena cava as the bolus of contrast agent travels towards the heart. *H*, Head; *F*, Feet.

microspheres [GENM]). The echogenicity of this gas containing contrast agent is based on the presence of multiple solid-gas interfaces with a large acoustic impedance mismatch. Several sizes of GENM (80, 76, and 12 μm) were injected intra-arterially while imaging over normal organs (liver and kidney) and VX2 tumors implanted within the rabbit thigh or kidney. Intravenous injections were prohibited because of the large size of the particles. GENM are seen as highly echogenic particles flowing through large vessels. Because of their size, the particles are trapped within normal parenchyma and at the vascular margins of tumors, producing enhancement that persists for several minutes.

Sonication of 5% human serum albumin* produces a gas-filled microbubble that is small (3 to 5 μm) and stable enough to allow free passage through the pulmonary capillary circulation. Particle concentration is high (4×10^8 spheres/ml). The agent is available prepackaged in ready-to-use 4 ml vials. It has a clinically useful shelf life of 6 months. Albunex has caused no clinically significant hemodynamic effect or toxicity in animal or patient studies.[38-40] Following intravenous administration, the agent's microbubbles rapidly dissolve (half-life less than 1 minute), and the residual free albumin is taken up by the Kupffer cells of the liver.

Cardiac applications of Albunex are the most promising. Albunex crosses the pulmonary bed and opacifies the left atrial and ventricular cavities[38,39,41] (Fig. 3-4). Following intracoronary injections, perfused myocardium increases markedly in echogenicity, allowing quantification of myocardial perfusion.[40,42] Many potential cardiac applications can be proposed, including delineation of endocardial borders, calculation of left-ventricular ejection fraction, quantification of regurgitant and shunt lesions, and enhancement of low-intensity Doppler signals.[43] Although Albunex arrives intact in the systemic arterial tree, the concentration of the agent is far less in the left ventricle than in the right ventricle. A significant amount of agent is trapped and/or destroyed during its passage through the lungs, cardiac chambers, and valves. Quantitative studies of the loss of the agent as it traverses the heart and lungs are not, as yet, available.

Albunex has been studied with abdominal imaging in small animals. It is not yet approved f r human use. With conventional gray-scale imaging, visualizati n of the contrast agent within large and small arteries r a change in the tissue echogenicity f the liver and kidney has not been identified following intravenous injection.[44,45]

*Albunex, Molecular Biosystems, Inc., San Diego, California

A B C D

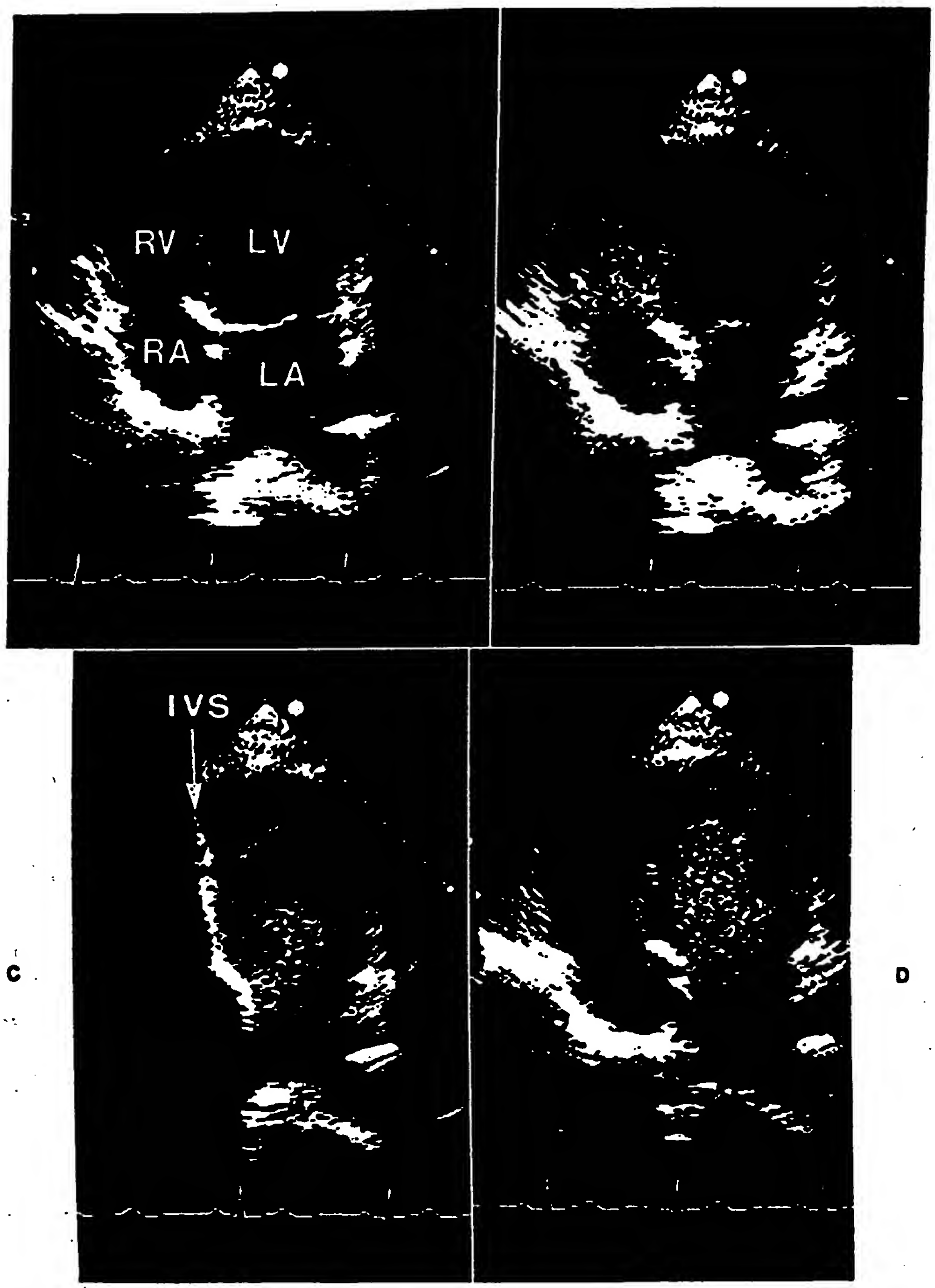
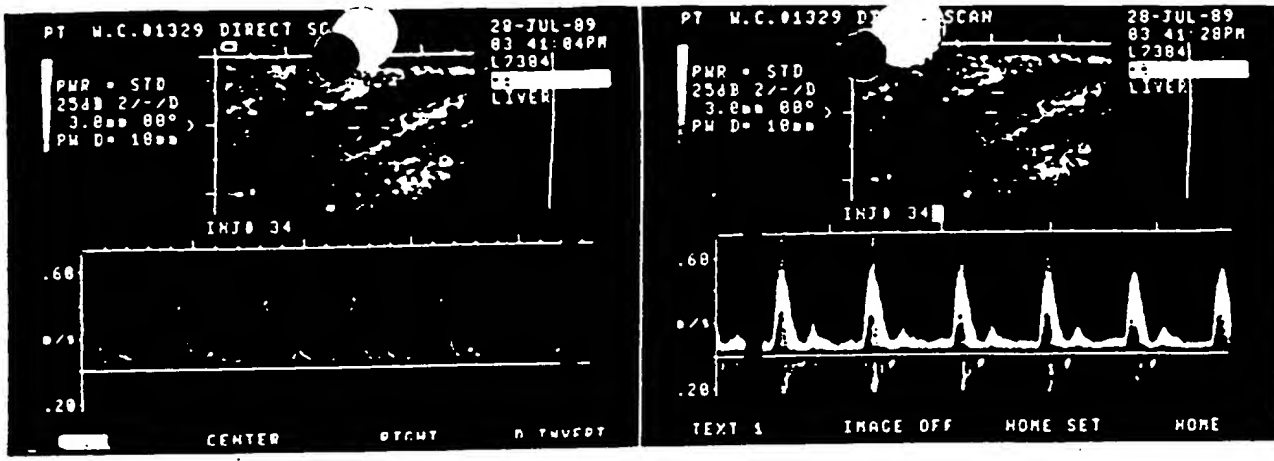
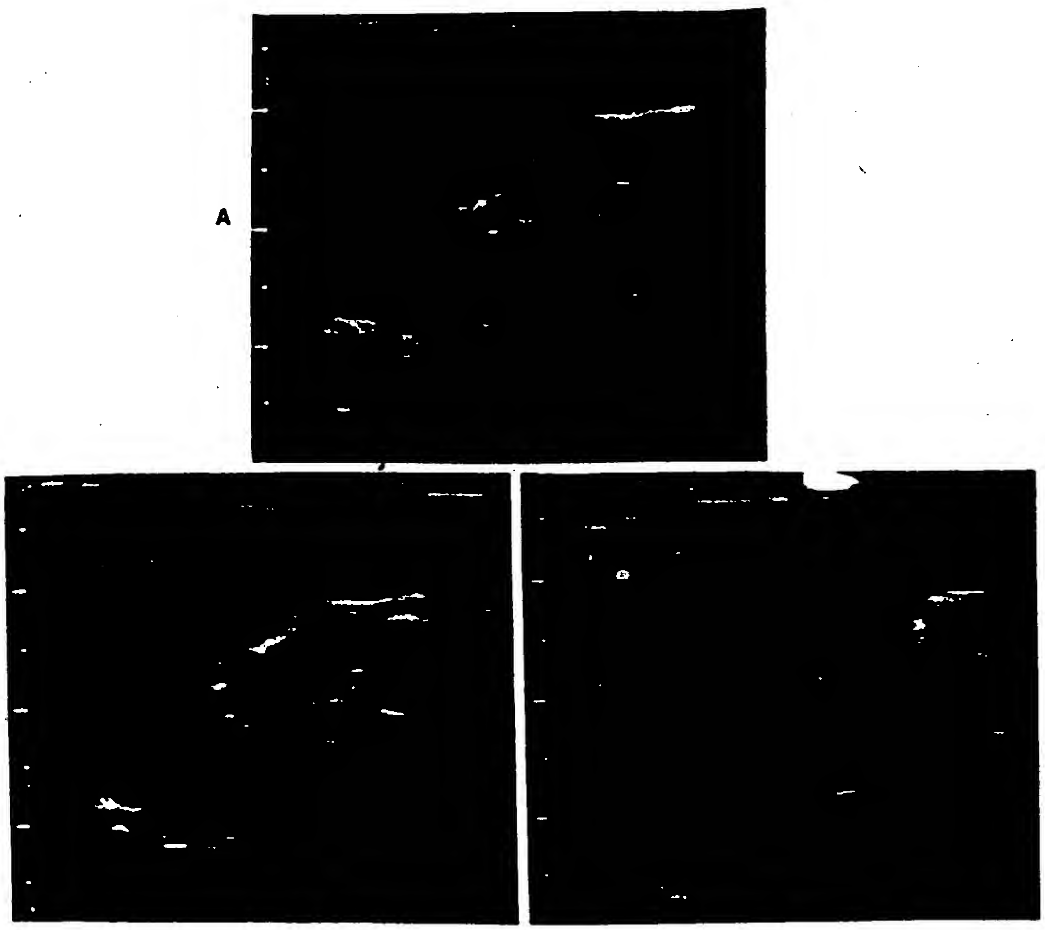


FIG 3-4. Opacification of the cardiac chambers using Albunex. A, Four chamber view of the heart before administration of intravenous Albunex. *RV*, Right ventricle; *RA*, Right atrium; *LV*, Left ventricle; *LA*, Left atrium. B, The echogenic microspheres first opacify the right atrium and right ventricle. C, Several seconds later, Albunex opacifies the left atrial and left ventricle chambers. Note that the high concentration of microbubbles within the right-sided cardiac chambers produce significant attenuation of the sound beam. *IVS*, Interventricular septum. D, The concentrati n of Albunex decreases in the right ventricle and increases in the left ventricle, improving delineation f the hypoech ic myocardial borders (*).
(Courtesy of Joel R. Raichlen, Philadelphia, PA.)



A B

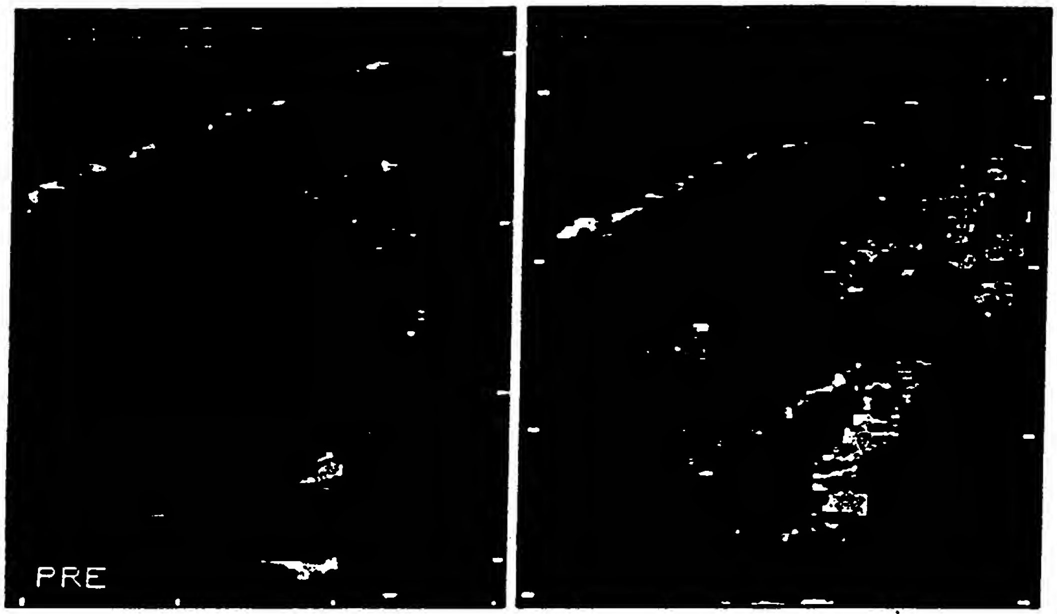
FIG 3-5. Spectral Doppler enhancement with Albunex. Sagittal image of the woodchuck aorta, A, before, and B, after the intravenous administration of 0.2 ml/kg Albunex shows marked of the septral Doppler signal intensity.



A B C

FIG 3-6. Renal cortical col r Doppler enhancement following Albunex administration. Transverse images through the renal hilum of a woodchuck kidney, A, before, and after, B, the intraven us administrati n f 0.2 ml/kg Albunex sh ws enhancement of the central renal arteries (coded in red). Tw seconds later, at a l wer transverse image of the kidney, C, dense c rtical color Doppler enhancement is present lasting 5 to 6 seconds.

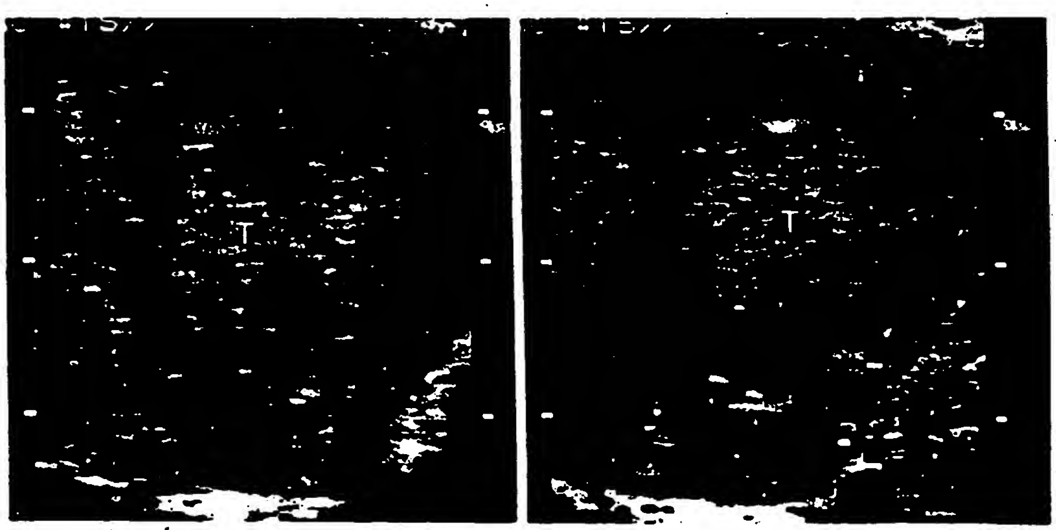
A



B

FIG 3-7. Cortical color Doppler enhancement improves the delineation of a renal mass. **A,** Color Doppler preinjection image through the upper pole of the right kidney in a rabbit with an implanted VX2 tumor shows a slight cortical bulge and loss of the normal cortical medullary distinction *(arrows)*. **B,** Following 0.3 ml/kg of Albunex, dense color Doppler enhancement of the normal renal cortex occurs. The hypovascular mass does not enhance, improving detectability of the mass.

A



B

FIG 3-8. Peripheral vascular enhancement of a woodchuck hepatoma using Albunex. **A,** Transverse image through the hepatoma shows the ill-defined tumor to be of mildly increased echogenicity *(arrows)* relative to the adjacent normal parenchyma. Minimal color Doppler signal from the peripheral vessels is noted. **B,** After the intravenous injection of 0.2 ml/kg f Albunex, dramatic color Doppler enhancement of the peripheral vessels of the tumor occurs.
(From Goldberg BD, Hilpert PL, Burns PN et al, with permission.)

However, pronounced Doppler signal enhancement is produced in arteries of all sizes by both qualitative[44] and quantitative[45] methods (Fig. 3-5). Significant dose-related Doppler signal enhancement can be documented by both pulsed and color Doppler. The degree of signal augmentation is such that, with larger doses, parenchymal color Doppler enhancement, reflecting capillary blood flow, can be identified (Fig. 3-6). Typically, such signals are below the power threshold for conventional Doppler equipment. Use of a Doppler-enhancing agent with color Doppler technology, providing a global picture of organ vascularity, may allow the identification of perfusion abnormalities caused by vascular occlusions, vascular displacement, tissue replacement by masses of altered vascularity (Fig. 3-7), and tumor neovascularity (Fig. 3-8).

COLLOIDAL SUSPENSIONS

Colloidal suspensions consist of solid particles suspended in a liquid carrier. These agents are selectively taken up by the reticuloendothelial system and lead to an increase in backscatter or attenuation of tissues. Many factors affect particle backscatter; among these are, primarily, the radius of the particle and, less so, the frequency of the imaging transducer, the density difference between the particle and the surrounding tissue, and the particle concentration.[7,8]

Collagen or Gelatin Spheres

Ophir et al examined the backscatter properties of 2 to 3 μm collagen[46] or gelatin[47] spheres in both in vitro and in vivo models. Backscatter measurements from suspensions of collagen microspheres and human blood standards showed that those containing collagen microspheres have a significantly greater (29.6 dB) echogenicity. Subsequent in vivo measurements, following intravenous injections into dogs, confirmed an increase liver echogenicity. The degree of backscatter enhancement in the in vivo preparation was much greater than predicted by the in vitro data, suggesting that other mechanisms may also play a role. One such mechanism may be particle reaction with circulating proteins to produce larger aggregates of particles within the Kupffer cells of the liver.[48]

IDE Particles

In vitro and ex vivo corroboration of initial work by Ophir et al[46,47] was performed by Violante et al,[49] using iodipamide ethyl ester (IDE) particles, which increase backscatter in the livers of rate. This is thought to be caused by colloid particles that are phagocytized by Kupffer cells present in normal liver but absent in tumors. Thus, detection f lesions that are hypoechoic or isoechoic to normal surrounding tissue should improve with IDE particles.

Perflu r chemicals (PFC)

Perfluorochemicals are a class of compounds composed entirely of carbon and fluorine atoms. These compounds were first introduced t the medical research community by Clark and Gollan,[50] who demonstrated their xygen-carrying capacity by submerging mice in the liquid for an extended period of time without ill effect.

Perfluorooctylbromide (PFOB)* is a type of PFC in which a bromine atom is substituted for a fluorine atom, resulting in a compound that is radiopaque[51-55] and nearly twice as dense as water, with a specific gravity of 1.9 gm/ml. It is emulsified in lecithin to produce a 100% weight-per-volume emulsion. The particles, 0.1 to 0.2 μm in size, are unable to leak out of normal capillaries, thus initially limiting the contrast to the intravascular space (Fig. 3-9). PFOB is removed from the bloodstream by the phagocytic function of the reticuloendothelial system of the liver and spleen, and later excreted by evaporation through the lungs without significant breakdown of the compound. The kidneys play no role in concentration or excretion of the compound.[56] The half-life of intravenous PFOB given to rats at a dose of 1.5 g/kg is 3 days, long enough to allow thorough radiologic investigation. Toxicity is low,[56] but not insignificant.[55] There are no cardiovascular or systemic hemodynamic effects following intravenous administration.[57,58] In a human clinical trial, side effects included pain in the lower back, fever and chills, reduced platelet count, mild cholestasis, and modification of blood lipid levels.[55]

PFOB-containing tissues are more echogenic, which is related to an increase in the number and brightness of reflectors. The increased echogenicity of PFOB is related to its high density (1.9 g/ml) and low acoustic velocity (600 m/s). This yields an acoustic impedance difference of 30% with non-PFOB-containing tissues, much greater than the typical impedance differences of 1% to 5% among various normal tissues and between normal and abnormal tissues. Although the particle size of PFOB falls well below the calculated optimum size for obtaining enhanced backscatter (0.8 to 2 μm at 5 MHz), agglomeration to other particles or to proteins within the vascular system or within the reticuloend thelial system may produce a larger effective particle size, resulting in altered echogenicity.[7,8]

Perfluorochemicals, particularly PFOB, have shown great promise as ultrasound and Doppler contrast agents.[59,60] Proposed applications of PFOB have been spearheaded by R.F. Mattrey et al, and include hepatic[61-63] and renal[64,65] ultrasound and computed tomography for detection of focal lesions, Doppler imaging for tumor blood flow,[65] blood pool ultras und im-

*Alliance Pharmaceuticals, San Diego, California.

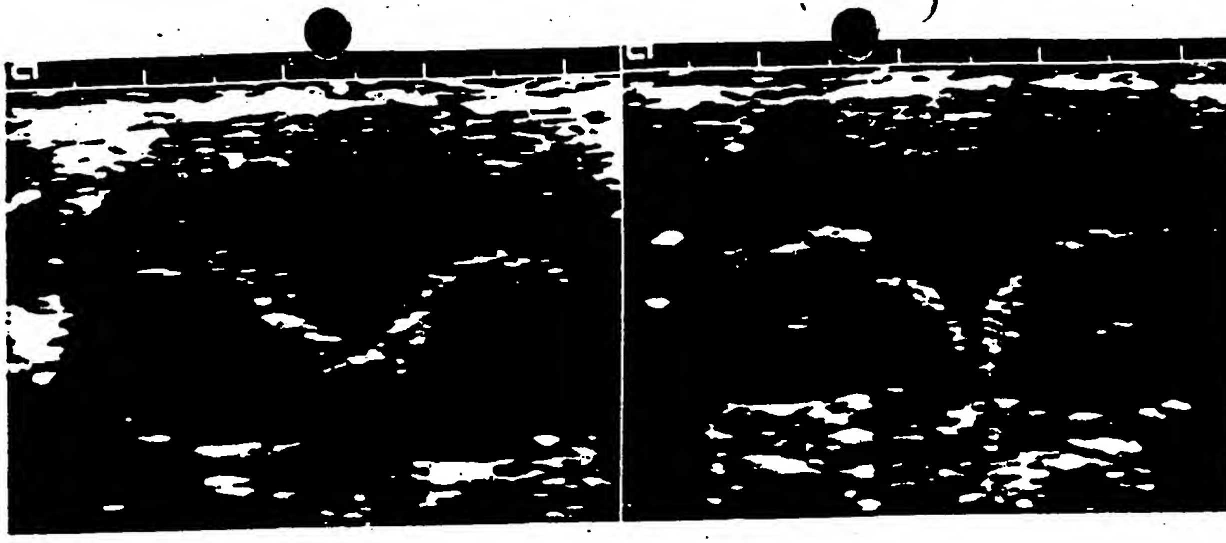


FIG 3-11. PFOB enhances diagnosis of acute tubular necrosis (ATN). A, After the intravenous administration of 5 ml/kg of PFOB, there is enhancement of the medullary portion of the normal kidney. The intact osmotic gradient across the medulla results in an increased concentration of PFOB in the vasa rectal. B, In the kidney with ischemia-induced ATN, the osmotic gradient is disrupted, resulting in lack of medullary enhancement.
(From Munzing D, Mattrey RF, Reznick VM, et al: The potential role of PFOB enhanced sonography of the kidney. Part I - Detection of renal function and acute tubular necrosis. *Kidney International*, in press, with permission.)

has been shown to accumulate in other immunologically active lesions, such as abscesses[69,70] and infarcted tissue.[71]

The normal osmotic gradient in the renal medulla causes hemoconcentration in the vasa recta, which causes increased concentration of PFOB and, therefore, increased echogenicity in the medullary portion of the kidney compared to the cortex. To study this process, Mattrey et al[67] subjected a group of rabbits to unilateral transient renal ischemia. The resulting acute tubular necrosis disrupted the normal concentration gradient of the renal medulla. The disruption of the concentration gradient was not apparent on precontrast images, but was identified by a lack of medullary enhancement after the administration of PFOB.

Because PFOB can be used as a blood-pool sonographic imaging agent, perfusion defects within an organ may also be mapped. Rabbits were subjected to partial renal embolization. Before the administration of PFOB, gray-scale imaging did not detect the infarcted kidneys and color Doppler imaging correctly detected only 10% of renal infarcts. After the administration of PFOB, gray-scale imaging and color Doppler imaging allowed correct detection of all infarcted kidneys, since the perfused areas were significantly enhanced by the contrast (Fig. 3-11).[66]

Advantages of PFOB include its long half-life, allowing thorough imaging, gray-scale changes in echogenicity proporti nal to blood flow, both color and spectral Doppler enhancing properties, reticuloend thelial system update, and potential to be used in conjunction with computed tomography. The major limitations of PFOB include possible side effects and the complex relation of preinjection sonographic appearance of parenchymal lesions to the dynamic role of PFOB, including perfusion imaging, reticuloendothelial system deposition, and macrophage imaging.

LIPID EMULSIONS

Because excess fat deposition in hepatocytes produces enhanced backscatter,[72,73] lipid emulsions have been evaluated as ultrasound contrast agents.[74] It was hypothesized that transient hepatic lipid accumulation would lead to increased echogenicity of normal liver parenchyma compared to abnormal parenchyma. However, preliminary studies using intravenous lipid emulsions suggest that a perceptible difference in echogenicity between control and lipid-containing livers has not been readily achieved, apparently because of their small particle size and relatively low concentration within the liver.

AQUEOUS SOLUTIONS

The introduction of solutions into the bloodstream to enhance ultrasound backscatter and reflectivity from tissues was first proposed by Ophir et al.[75] Some aqueous solutions show a linear increase in the speed of sound propagation and density as a function of the molar concentration.[76] Therefore the acoustic impedance, the product of density and velocity (the speed of sound through tissue), is a function of concentration. Ophir et al[75] have sh wn that a transient acoustic impedance

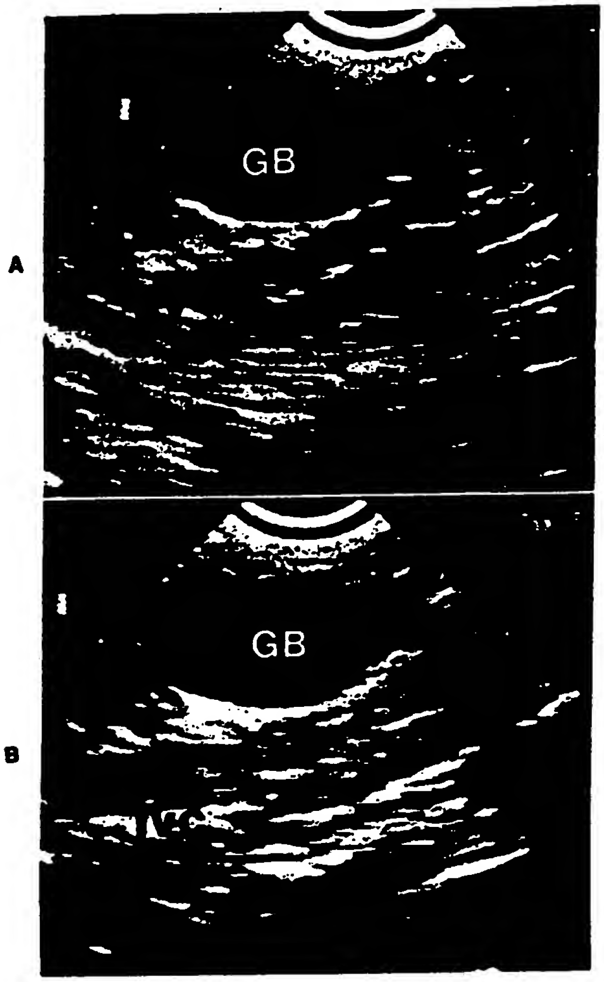


FIG 3-9. A PFC opacifies venous blood flow. A, In a preinjection sagittal image of the right upper quadrant of a woodchuck, the portal vein *(PV)* and inferior vena cava *(IVC)* are anechoic due to the presence of flowing blood. B, Shortly after the administration of 5 ml/kg of a PFC solution, dense and persistent echoes are identified within the *PV* and *IVC*. *GB*, Gallbladder.

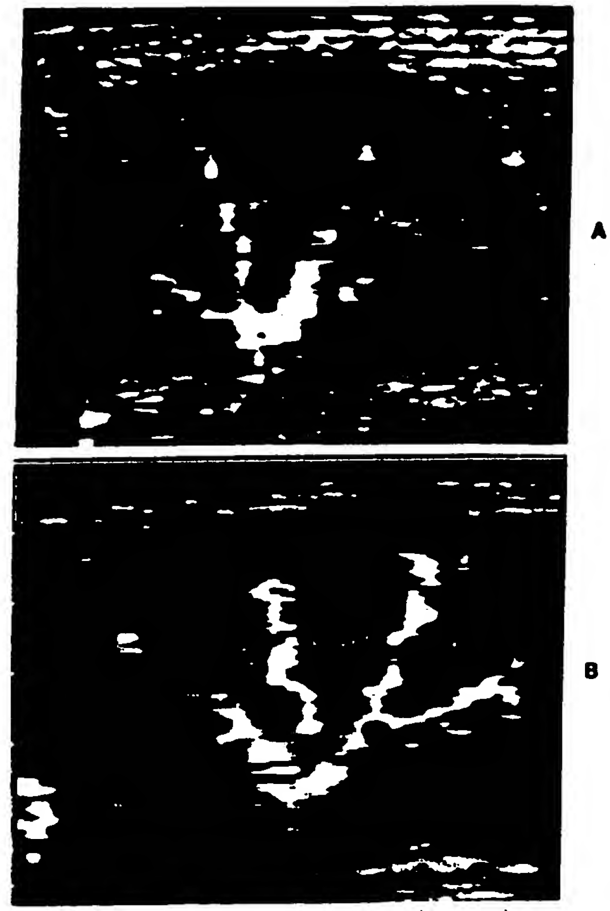


FIG 3-10. PFOB produces vascular enhancement. A, Baseline color Doppler image of a rabbit kidney. B, Shortly after intravenous administration of 2 ml/kg of PFOB, there is profound enhancement of the vascular signal, including visualization of the accurate ring and small cortical vessels.
(From Coley BD, Mattrey RF, Roberts A, et al: The potential role of PFOB enhanced sonography of the kidney. Part II—Detection of partial infarction. *Kidney International*, in press, with permission.)

aging for organ perfusion,[66] and assessment of renal concentrating ability.[67]

Following the intravenous injection of PFOB, the stages of parenchymal and tumor enhancement on ultrasound vary with time. Initially, as PFOB is contained within the intravascular space, the degree of enhancement of an organ is related to the degree of organ perfusion (Fig. 3-10). For example, relatively hypovascular renal tumors that are isoechogenic with the kidney become more apparent (relatively less echogenic) after the administration of PFOB because the normal kidney increases in ech genicity in proportion t its blood supply.[64] As the contrast agent is fixed by the reticuloendothelial system, the normal liver and spleen increase in echogenicity.[61-63] Hepatic tumors and abscesses, which were typically less echogenic or isoechogenic with normal surrounding parenchyma, appear relatively more hypoechoic after the administration of PFOB. These focal lesions, which lack reticuloendothelial system function, do not take up the contrast agent as normal surrounding parenchyma, resulting in increased contrast differences between normal and abnormal tissues and improved lesion detection.[61-63] With both ultrasound and computed tomography, enhancement of the margin of VX2 tumors in rabbits has been identified as a late finding (1 to 2 days foll wing administration) and attributed to the deposition f PFOB-containing macrophages at the tumor periphery.[61,68] Additionally, PFOB

A

B

FIG 3-12. Partial renal infarction detected with PFOB. A, Precontrast coronal image of a rabbit kidney, following segmental infarction is normal. B, Following the intravenous administration of 3 ml/kg PFOB, a hypoechoic, wedge-shaped infarct is identified because of enhancement of the remainder of the kidney.
(From Coley BD, Mattrey RF, Roberts A, et al: The potential role of PFOB enhanced sonography. Part II — Detection of partial infarction. *Kideny International*, in press, with permission.)

mismatch is created between the vascular and nonvascular beds in the time immediately following an intravenous injection of an agent with a significantly different acoustic impedance from normal body tissues. Materials that bear a strong dependence of the speed of sound on concentration and have a low toxicity include buffered sodium citrate, calcium gluconate, and calcium disodium EDTA.[77] In vitro and in vivo investigations[75,77] have supported these assumptions, showing transient renal cortical echo enhancement following intravenous injections f these soluti ns.

FUTURE DIRECTIONS

Several contrast agents offer great promise for improved diagnostic accuracy. Each agent offers slightly different applications, tailored to its physical characteristics. SH U 454 is an agent that because of its short half-life is suited for venous imaging and for intracavitary uses. With the development of SH U 508, which is more stable agent capable of transpulmonary passage, alterations in parenchymal echogenicity or systemic arterial Doppler enhancement may be identified. Encapsulated human albumin microspheres (Albunex), which also have a short half-life are most useful for flow imaging with color Doppler, allowing improved detection of small or deep vessels, distinction between high-grade stenosis and complete occlusion, and identificati n of neovascularity. Basic research shows PFOB to be a useful contrast agent for sonographic tumor and abscess detection in the liver and tumor detection in the kidney. Presently, PFOB is undergoing clinical trials in Europe. Because PFOB enhances the Doppler signal of n rmal vascular structures, vascular displacement, occlusion, and tumor vascularity are more easily appreciated by both duplex and color Doppler imaging. Additi nally, PFOB may be used as a blood-pool agent to assess, in a dynamic fashion, the concentration gradient of the tubules in the renal medulla.

To date, ultrasound contrast agents are essentially experimental. Given the lower cost and greater worldwide availability of sonography over other imaging modalities (computed tomography and magnetic resonance imaging), the need for a contrast agent is great.

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